

Continuous Improvement under Modern Quality Systems and CGMPs

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“Plan for Meeting Needs of Tomorrow”

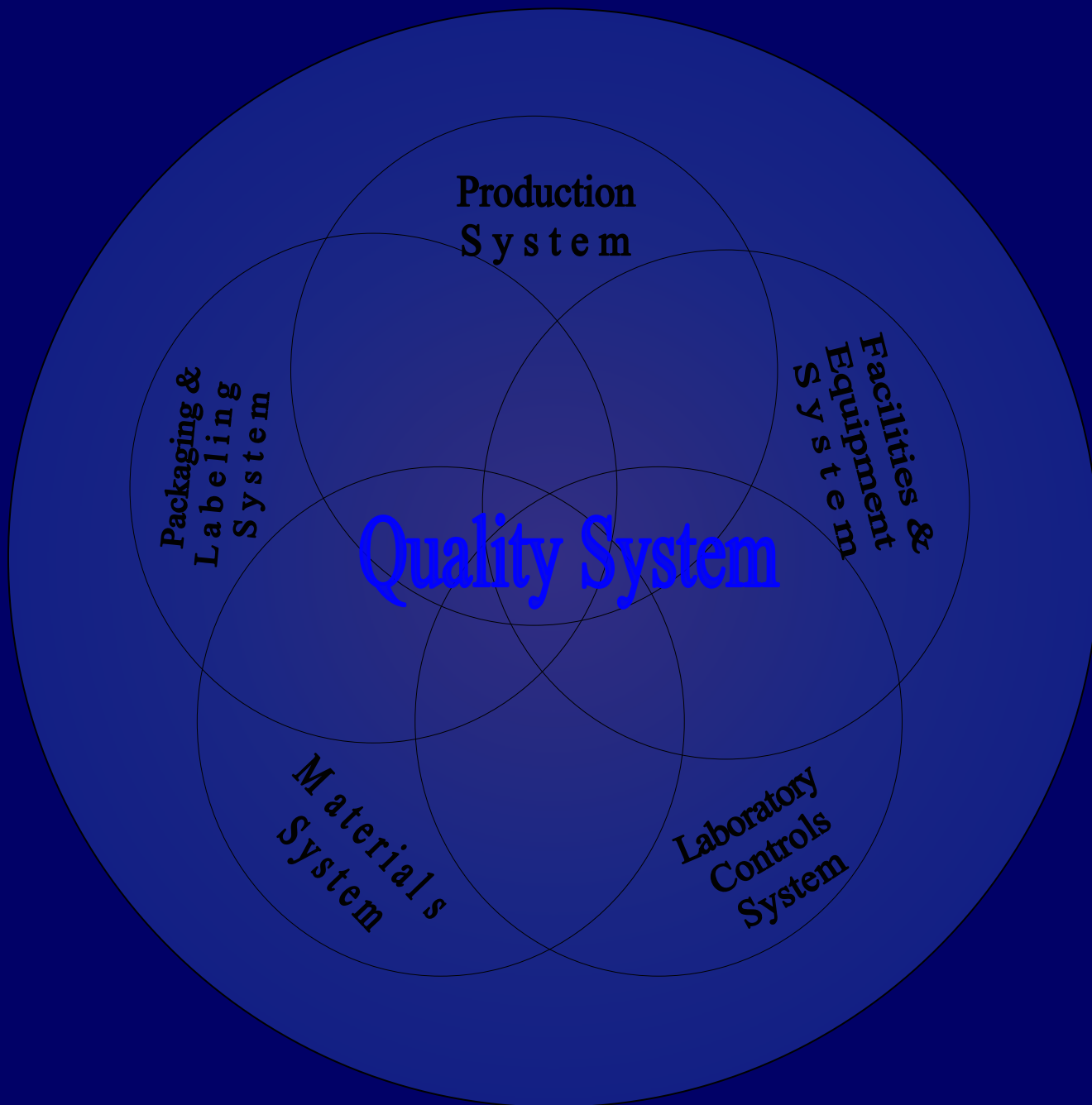
“Under the leadership of the Council on Pharmaceutical Quality...

- Develop *additional guidance on quality systems for pharmaceutical manufacturing* so that the Agency’s goal to enhance and modernize the regulation of pharmaceutical manufacturing and product quality is met.
- Continue development of the risk-based pharmaceutical quality assessment system that will replace the current CMC review system to *remove hurdles to continuous improvement following drug approval.*”

Quality Systems

Industry Guidance: Quality Systems Approach to CGMP Regulations (draft, 9/04)

- Intent of guidance is to help manufacturers meet requirements of the Agency's current good manufacturing practice (CGMP) regulations (21 CFR parts 210 and 211) using a comprehensive quality systems approach.
- It discusses how modern, comprehensive quality systems provide for full compliance with CGMP regulations. The guidance cross-references how and where specific CGMP regulations fit within the comprehensive QS model.



Quality System

Each of these are integral to continuous learning throughout product lifecycle:

1. *Science-based* approaches
2. Decisions based on *understanding product's intended use*
3. Proper identification and control of areas of *potential process weakness* (including raw materials)
4. *Responsive deviation and investigation* systems that lead to timely remediation
5. Sound methods for *assessing risk*
6. *Well-defined and designed processes and products*, from development through entire product life cycle.
7. *Systems for careful analyses* of product quality
8. *Supportive management (philosophically and financially)*

Basic Quality System Attributes Assessed in Inspections

- “The inspection is defined as audit coverage of 2 or more systems, with mandatory coverage of the Quality System.”
- “The system assures overall compliance with cGMPs and internal procedures and specifications.”

Basic Quality System Attributes Assessed in Inspections (*cont'd*)

For example:

- Does Quality Control Unit (QCU) fulfill responsibility to review and approve procedures and assure adequacy?
- Does firm assure adherence to written procedures?
- Handling of annual reviews, complaints, discrepancy/failures
- Effective Change Control Program
- Validation
- Training/qualification of employees in QCU functions

Strong Quality System: Benefits for Manufacturer

- Firms with strong Quality Systems (QS) will:
 - gain process understanding
 - continuously improve
 - meet and exceed CGMPs
 - benefit from reduction of supplements
 - have sound change control programs that “manage change to prevent unintended consequences”

**Quality by Design
and
Continuous Improvement**

Continuous Learning & Improvement Only Happens When There is Commitment

- *“Being busy does not always mean real work. The object of all work is production or accomplishment and to either of these ends there must be forethought, system, planning, intelligence, and honest purpose, as well as perspiration. Seeming to do is not doing.”*

(Edison)

- *“It is not only for what we do that we are held responsible, but also for what we do not do.”*

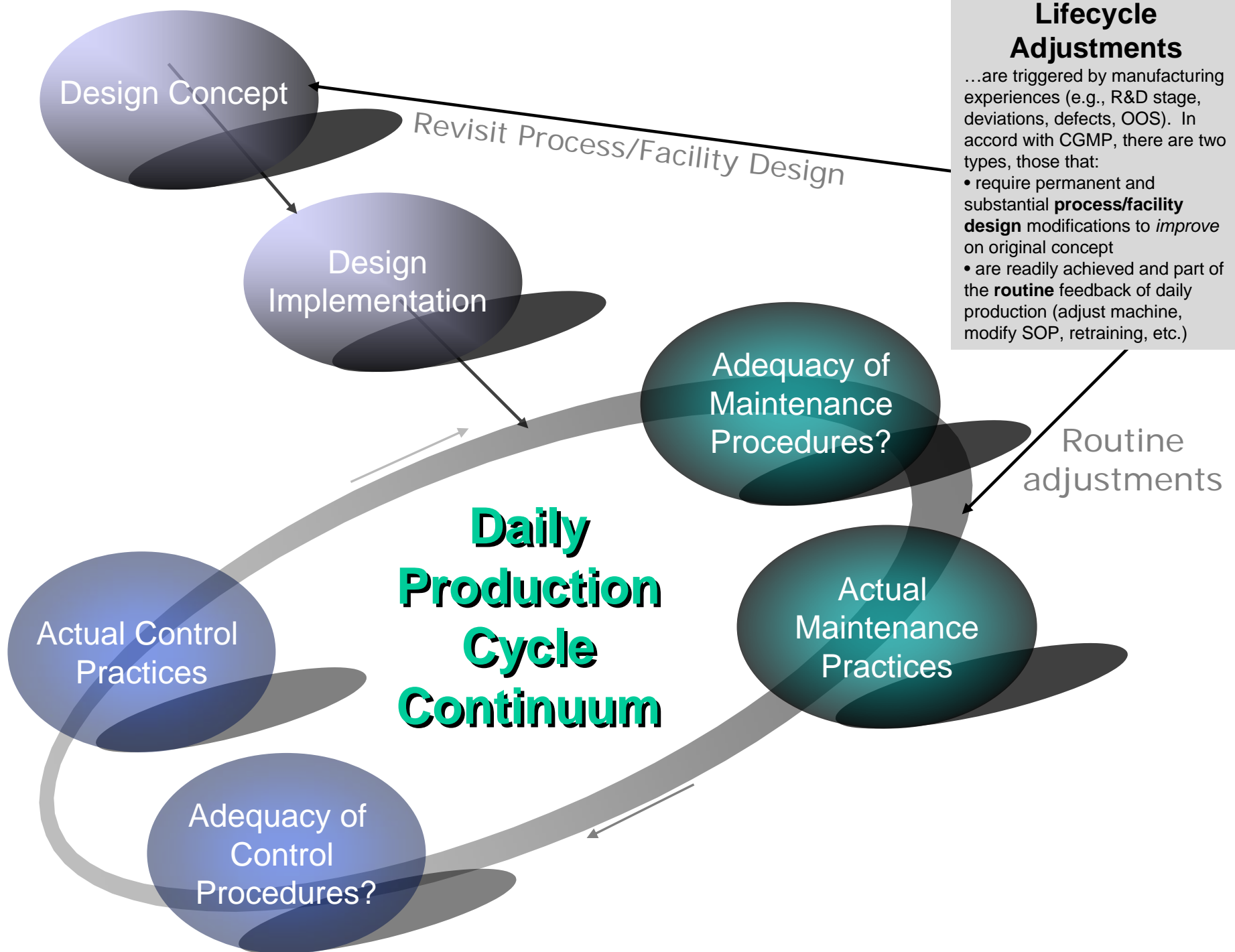
(Moliere, 17th Century)

Continuous Improvement

Manufacturers with appropriate process knowledge and a robust quality system should be able to implement many types of **improvements** without the need for prior regulatory filing. In addition, an effective quality system, by lowering the risk of manufacturing problems, can decrease the length and frequency of inspection coverage.

“Design Quality In”

- Also known as “Design for Quality” or “Quality by Design (QbD)”
 - Well-established industrial quality concept
- “Design” mentioned 18 times in the CGMP Regulations
- Emphasized in our 21st Century Initiative and Strategic Plan



Enhanced Process Understanding



Design/Refine for Quality



Process Consistency

Ongoing QS Vigilance:

Some reasons why its

important

Some Raw Material Considerations

- Have raw materials been named as the cause of product failures at your firm?
- Can what seems to be an innocuous alteration in the supplied material ultimately affect finished product quality?
 - In 2005, are some influential raw material characteristics still “invisible?”
- While all raw materials should receive appropriate surveillance, a strong vendor qualification program should likely afford most scrutiny to the following to increase likelihood of preventing such problems:
 - less reliable or “unproven” vendors
 - those that produce the most critical or complex raw materials

Some Raw Material Considerations (*cont'd*)

- Does vendor operate under GMP systems in their labs and production departments?
 - Does vendor have a reliable change control *and* notification system?
 - Is the Quality Agreement adequate?
- Are the Vendor's operations underpinned by good science?
 - How reliable are their data, studies, and conclusions?

Good Science

- Scientific Basis for rational CGMP decision-making
 - *Via sound experimentation and observation*
 - *Objective conclusions*
 - *Underpins CGMP*
 - *References*
 - *replicated research? applicability?*
 - *Ultimately, good science leads to enhanced understanding of a given process or system and its uniqueness/vulnerabilities*

Why Good Science is Fundamental to Good Manufacturing Practice

- Appropriate study design
 - Meaningful study outcomes (e.g., product/process development and validation studies)
- Facilitates “Building Quality In”
 - Knowledgeable decisions on operational design, raw material inputs
- Sound change control evaluations
- Proper Supervisory/QA oversight
 - Audits and supervisory decisions based on understanding product and process

Why Good Science is Fundamental to Good Manufacturing Practice

- Management Responsibility
 - Solid feedback loops provide for fact-based decision-making
- Investigations
 - Sound strategies and tools for determining root cause
 - CAPA decisions founded in technical understanding of process and awareness of product characteristics (e.g., physiochemical attributes and sensitive; intended clinical use)

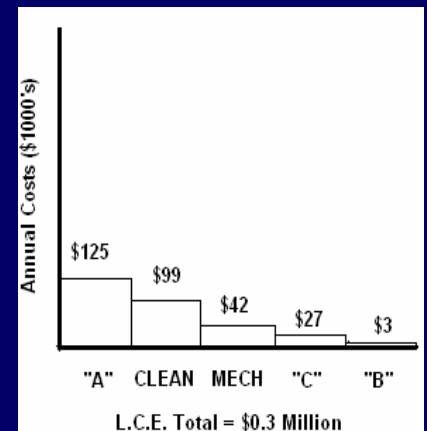
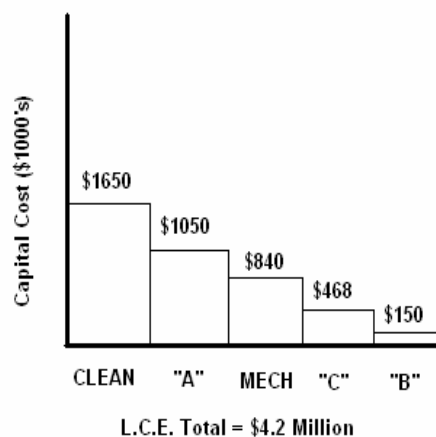
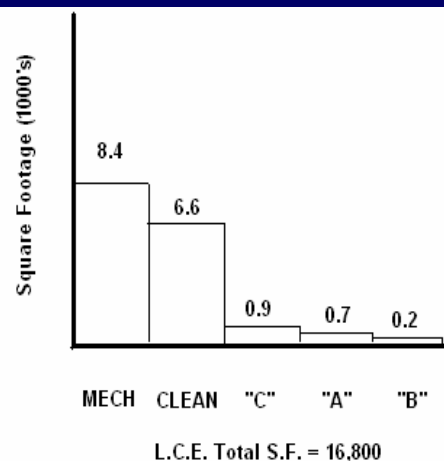
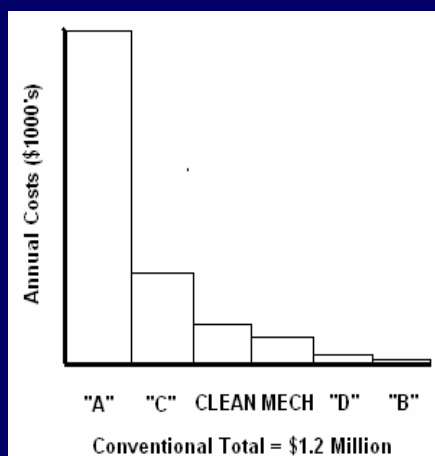
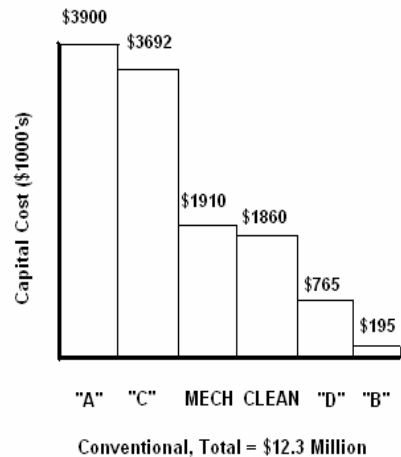
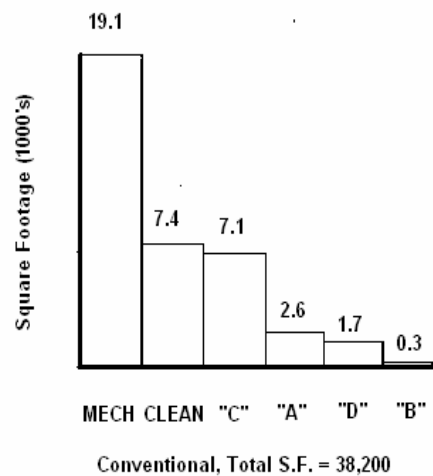
The Role of Modernization in the Quality System

Modernization = Risk Mitigation

- **Better Operational Design**
 - More robust equipment and facilities (e.g., isolators)
 - Process predictability and reliability is a major theme of the 21st Century initiative
- **Improved Testing**
 - More rapid problem detection and remedies
- **Quality/Business Synergies**
 - Robust operational design and good metrics/testing is fundamental to a good Quality System
 - Beneficial to “Design for Quality” from the outset

The Quality-Business Synergy

- Increase product and process understanding (better decisions)
- Minimize product variability (better products)
- Enhance test method accuracy and precision (better information)
- Reduce costs due to investigations, deviations, and rejections
- Minimize product loss and associated costs (i.e., scrap, disposal, rework, recall)
- Reduce downtime via more reliable equipment and less repair interruptions
- Decrease number of personnel (e.g., via automation) needed to conduct operations



GROSS SQ. FOOTAGE

CAPITAL COSTS

ANNUAL ENERGY COSTS

(Source: M. Porter, ISPE Barrier Isolator Conference, Zurich, 1995)

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For More CGMP Information...

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*CDER CGMP technical specialists:
<http://www.fda.gov/cder/dmpq/subjcontacts.htm>*